Neuroprognostication, withdrawal of care and long-term outcomes after cardiopulmonary resuscitation

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Purpose of review
Survivors of cardiac arrest often have increased long-term risks of mortality and disability that are primarily associated with hypoxic-ischemic brain injury (HIBI). This review aims to examine health-related long-term outcomes after cardiac arrest.

Recent findings
A notable portion of cardiac arrest survivors face a decline in their quality of life, encountering persistent physical, cognitive, and mental health challenges emerging years after the initial event. Within the first-year postarrest, survivors are at elevated risk for stroke, epilepsy, and psychiatric conditions, along with a heightened susceptibility to developing dementia. Addressing these challenges necessitates establishing comprehensive, multidisciplinary care systems tailored to the needs of these individuals.

Summary
HIBI remains the leading cause of disability among cardiac arrest survivors. No single strategy is likely to improve long term outcomes after cardiac arrest. A multimodal neuroprognostication approach (clinical examination, imaging, neurophysiology, and biomarkers) is recommended by guidelines, but fails to predict long-term outcomes. Cardiac arrest survivors often experience long-term disabilities that negatively impact their quality of life. The likelihood of such outcomes implements a multidisciplinary care an integral part of long-term recovery.

Keywords
cardiac arrest, hypoxic-ischemic brain injury, long-term outcomes, neuroprognostication

INTRODUCTION

Worldwide estimates of the incidence of out-of-hospital cardiac arrest (OOHCA) were 55 cases per 100 000 person-years more than two decades ago. The average survival rate to hospital discharge was 7% at that time [1]. In 2022, the ongoing CARES registry reported an incidence of 88.8 per 100 000 of nontraumatic arrests, with a median age of 65.0 years [2]. For survivors of arrest, the most troubling aspect is the likelihood of death and disability after cardiac arrest, which remains related to the initial hypoxic-ischemic brain injury (HIBI) [3–5]. Several strategies have been tried to limit the damage caused by HIBI; however, most fail to show significant long-term improvement.

Long-term outcomes in cardiac arrest survivors are commonly assessed using neurological function scores, such as the Cerebral Performance Category score (CPC), and the modified Rankin Score (0–6), as well as health related quality of life (HRQL) questionnaires (i.e. HUI, SF-36, and EQ-5D-5L) [4] (see Table 1). Studies have shown that cardiac arrest and ICU survivors experience substantial impact across physical, cognitive, neurological, emotional, and social domains years after the initial event or hospital discharge, underscoring the need for the implementation of comprehensive care systems in the management of cardiac arrest, which is crucial for improving long term outcomes and health-related quality of life (HRQoL) among survivors.

INTERVENTIONS TARGETING HYPOXIC-ISCHEMIC BRAIN INJURY

Since HIBI remains the leading cause of mortality and disability after cardiac arrest, attempts at preventing and alleviating it are key [6]. Early studies focused on neurological outcomes tried to temper

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KEY POINTS

- Cardiac arrest survivors may experience long-term physical, mental, and cognitive impairment.
- Patients who survive cardiac arrest with a poor neurological outcome have lower survival rates and a higher risk for readmissions.
- Current guidelines on postresuscitation care are not based on neurprognostication for predicting long-term outcomes after cardiac arrest.

the severity of the hypoxic-ischemic injury during CPR. Devices such as the compression-decompression device [7], mechanical CPR (LUCAS) [8,9], and techniques such as abdominal counterpulsation [10] have been tried. Additionally extracorporeal cardiopulmonary resuscitation (ECPR) is currently being studied [11–13] (see Table 2). However, none of these devices or techniques successfully passed the early time point of outcome assessment at the time of hospital discharge.

Targeted temperature management

Some clinical trials have shown improvement in neurological outcomes at hospital discharge in patients treated with hypothermia [14▪], others have failed to show significant improvement beyond the 6-month mark. May and colleagues showed that moderate hypothermia (31°C), when compared to mild hypothermia (34°C), does not significantly reduce mortality, and improve neurological outcomes at 6 months [15]. Additionally, another study did not find a significant improvement regarding mortality and neurological outcomes after hospital cardiac arrest in patients treated with hypothermia versus normothermia [16]. A more recent systematic review of nine randomized clinical trials, found that neurological prognosis was significantly better in patients who received early targeted temperature management (<120 min) with a duration of more than 24 h, even though mortality rates did not differ between this group and the normothermia group. [17▪▪]. However, none of the included RCT's provided data on long term follow-up beyond 6 months.

Table 1. Commonly used scores for the assessment of long-term neurological outcome and health-related quality of life in cardiac arrest survivors

Functional assessment of long-term outcomes after cardiac arrest.			
Cerebral category score		**Modified Rankin scale**	
1	Good cerebral performance	0	No symptoms
2	Moderate cerebral disability	1	No significant disability
3	Severe cerebral disability	2	Slight disability
4	Coma or vegetative state	3	Moderate disability
5	Brain dead	4	Moderately severe disability
NA		5	Severe disability
NA		6	Dead
Health-related quality of life assessment questionnaires			
Questionnaire	Description		Score
HUI_3[a]	Instrument that evaluates 8 categories: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain		A score of 0.00 represents dead while a score of 1.00 indicates perfect health
SF-36[b]	36 item health survey consisting of 8 categories: physical functioning, role limitations due to physical health and emotional health, energy/fatigue, emotional well being, social functioning, pain, and general health.		Scores range from 0–100, where higher a higher score indicates a better health status
EQ-5D-5L	Health survey that consists of a descriptive system which encompasses mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and a visual analog scale.		The descriptive system generates a 5-digit number that ranges from 11111 (full health) to 55555 (worst health)

[a]The Health Utilities Index.
[b]Short Form Health Survey.

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Table 2. Assessment of CPR devices and techniques: corresponding time points in clinical trials

CPR Technique	RTC	Primary end point	Time points assessed	Significance
CO-AACD versus standard CPR	Li *et al.*, 2022 [10]	Time to ROSC	Survival to hospital admission and discharge	Improved survival to hospital discharge in the CO-CPR group
CO-AACD versus standard CPR	Yingxin *et al.*, 2018 [9]	Neurological outcome	3 months	Improved neurological outcome at 3 months with AACD-CPR
ECPR	Rob *et al.*, 2022 [11]	Survival	6 months	Survival rate of 23.9% in the ECPR group. Improved survival in patients without prehospital ROSC
ECPR	Pudil *et al.*, 2023 [12]	Survival in refractory OOHCA due to PE with good neurological outcome	30 days 6 months	No difference in outcome at 6 months between ECPR and standard CPR
ECPR	Nakashima *et al.*, 2019 [13]	Neurological outcome in refractory OOHCA	1, 2 and 6 months	Improved neurological outcome at 6 months in patients with FV/TV as initial rhythm
Mechanical CPR (LUCAS)	Marti *et al.*, 2017 [8]	Cost-efectivness of LUCAS HRQoL	3 and 12 months	LUCAS was associated with poorer health outcomes
Mechanical CPR (LUCAS)	Gates *et al.*, 2017 [9]	Survival without significant neurological impairment	30 days	Similar survival in LUCAS and manual CPR group

AACD, abdominal active compression decompression; CO, counterpulsation; ECPR, extracorporeal cardiopulmonary resuscitation; FV, ventricular fibrillation; HRQoL, health-related quality of life; ROSC, return of spontaneous circulation; VT, ventricular tachycardia.

EUROPEAN RESUSCITATION COUNCIL PROGNOSTICATION GUIDELINES VERSUS LONG-TERM OUTCOMES

The 2021 guidelines from the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) recommend a multimodal approach for neuroprognostication after cardiac arrest [18▪]. The proposed algorithm encompasses multiple diagnostic modalities (clinical examination, imaging, neurophysiology, and biomarkers) which should be performed three days after ROSC and in the absence of confounders, such as residual sedation, therapeutic hypothermia, neuromuscular blockade, severe hypotension, hypoglycemia, sepsis, and metabolic abnormalities [18▪]. The proposed criteria to establish prognosis derive from studies that evaluate neurological outcomes up to a maximum of 1 year and are summarized in Table 3.

LONG-TERM TRAJECTORIES OF RECOVERY AFTER CRITICAL ILLNESS AND CARDIOPULMONARY RESUSCITATION

Patients who have undergone intensive care treatment, as well as their families, are at risk for developing postintensive care syndrome (PICS). PICS encompasses a spectrum of physical, cognitive and/or mental health challenges [19]. It has been associated with several risk factors including older age, female sex, previous mental health problems, delirium, a negative ICU experience and disease severity [20].

In a comprehensive study involving 2345 ICU survivors, findings revealed that 58% of patients reported experiencing new mental and/or cognitive impairment within 1 year of hospital discharge. Notably, this trend was more common in urgent surgical patients [21]. In one prospective observational study ($n = 139$), 50% of patients developed PCIS at 3 months and 47% at 12 months. In this study, patients with poor neurological outcomes at hospital discharge had a higher risk for developing PICS [22]. Symptoms of PICS may exhibit different trends; an observational study in sepsis survivors revealed three different trajectories of depressive symptoms at 1, 6, and 12 months after ICU discharge. At 1 year, most patients recovered from mild symptoms, a smaller percentage of patients recovered from severe symptoms, while others experienced persistent and severe symptoms of depression, emphasizing the heterogenous nature of PICS [23]

Addressing PICS and recovery requires a multidisciplinary approach. Several interventions have been developed to minimize PICS including diaries, early mobilization, rehabilitation, and post ICU-recovery clinics [24]. Of these strategies, early rehabilitation proved to be efficient at improving only short-term physical outcomes but not long-term outcomes [25]. ICU recovery clinics can help ease the transition between ICU discharge and recovery

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Table 3. Duration of outcome evaluation in neuroprognostication studies following cardiac arrest

Neuroprognostication modality	Components	Studies	End point for neurological assessment
Clinical examination	GCS-M Pupillary light reflex Corneal reflex Status myoclonus	Sandroni *et al.*, 2020 [45]	Hospital discharge and 1 month
		Oddo *et al.*, 2018 [46]	3 months
		Moseby-Knappe *et al.*, 2020 [47]	6 months
		Solari *et al.*, 2017 [48]	1 year
Imaging	Generalized edema in brain CT/MRI	Wang *et al.*, 2018 [49] B. K. Lee *et al.*, 2016 [50] B. K. Lee *et al.*, 2015 [51]	Hospital discharge
		Kirsch *et al.*, 2021 [52]	30 days
		D. H. Lee *et al.*, 2018 [54] Moseby-Knappe *et al.*, 2017 [53] Scarpino *et al.*, 2019 [55] Hirsch *et al.*, 2020.	6 months
Neurophysiology	EEG SSEP	Westhall *et al.*, 2016 [56]	180 days
		Choi *et al.*, 2017 [57]	Hospital discharge
		De Santis *et al.*, 2017 [58]	3 months
		Dragancea *et al.*, 2015 [59] Dragancea *et al.*, 2017 [60] Grippo *et al.*, 2017 [61]	6 months
Biomarkers	NSE[a]	Streitberger *et al.*, 2017 [62]	Hospital discharge
		Vondrakova *et al.*, 2017 [63]	30 days, one year mortality
		Stammet *et al.*, 2015 [64] Wiberg *et al.*, 2017 [65]	6 months

EEG, electroencephalogram; GCS-M, Glasgow Coma Scale-Motor; NSE, neuron specific enolase; SSEP, somatosensory evoked potentials.
[a]The only biomarker recommended by guidelines.

and can help address the different issues in PICS in an individualized manner, with telemedicine emerging as a promising alternative for management [26].

LONG-TERM OUTCOMES AFTER CARDIAC ARREST

While the majority of cardiac arrest survivors experience improvement after hospital discharge, others can experience declines across physical, cognitive, and psychological domains that can persist for years after the initial event. In one study including OOHCA survivors with a GCS score >12 at 2 weeks after cardiac arrest revealed that 65% of individuals ($n = 98$) had a complete recovery or only minor disabilities at 18 months, 18% had moderate disabilities but were autonomous in daily life, 12% did not have autonomy. Importantly, significant improvement was noted before month 6 and less after this time point. Even though patients had a good neurological outcome, an impact on the HRQoL was still present, as 20% had cognitive impairment, 32% had anxiety, and 25% had depression [27]. In another study, 26% of patients ($n = 178$) reported experiencing impaired mobility, difficulty in maintaining personal hygiene, and in performing activities associated with daily life due to chronic pain, which occurred in 47.2% of patients, particularly those who survived for more extended periods of time [28]. Fordyce *et al.* found that in a population of 10 674 treated OOHCA, only 1325 survived hospital discharge. Three years after discharge, the survival rate was 84.1%. However, 31.8% of the discharged individuals remained alive and free from any readmissions within that time period. In addition, one of every four survivors required either residential or home care [29].

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Cognitive decline after cardiac arrest has been reported in multiple long-term studies. A recent study from the Danish Cardiac Arrest Survivorship survey found that 47% of cardiac arrest survivors ($n = 525$) experienced cognitive decline, as reported by observers [30▪▪]. This study used the Informant Questionnaire Cognitive Decline in the Elderly for Cardiac Arrest (IQCODE-CA), which was previously validated in a follow-up study of 268 patients of the TTM trial [31]. In both studies, cognitive decline was primarily associated with short-term memory impairments.

In a particular study, cardiac arrest survivors displayed elevated rates of stroke and epilepsy within the initial year postdischarge compared to a matched population with myocardial infarction. Additionally, individuals in the cardiac arrest cohort exhibited a heightened risk of developing dementia, with a 21-year risk of 73 per 1000 persons. Notably, similar patterns were observed when comparing this cohort to the general population [32▪] (Fig. 1). In the same study, cardiac arrest survivors also exhibited a higher risk for psychiatric conditions such as anxiety and depression when compared to myocardial infarction and general populations during the first year after the event. Significantly, these higher rates gradually declined over time to match those observed in the comparison groups [32▪]. In another study conducted in Singapore, cardiac arrest survivors demonstrated a higher cumulative incidence of subsequent acute myocardial infarction among OOHCA survivors than in the general population; in addition, older age at arrest presentation (>65 years) and previous acute myocardial infarction were significantly associated with subsequent acute myocardial infarction [33].

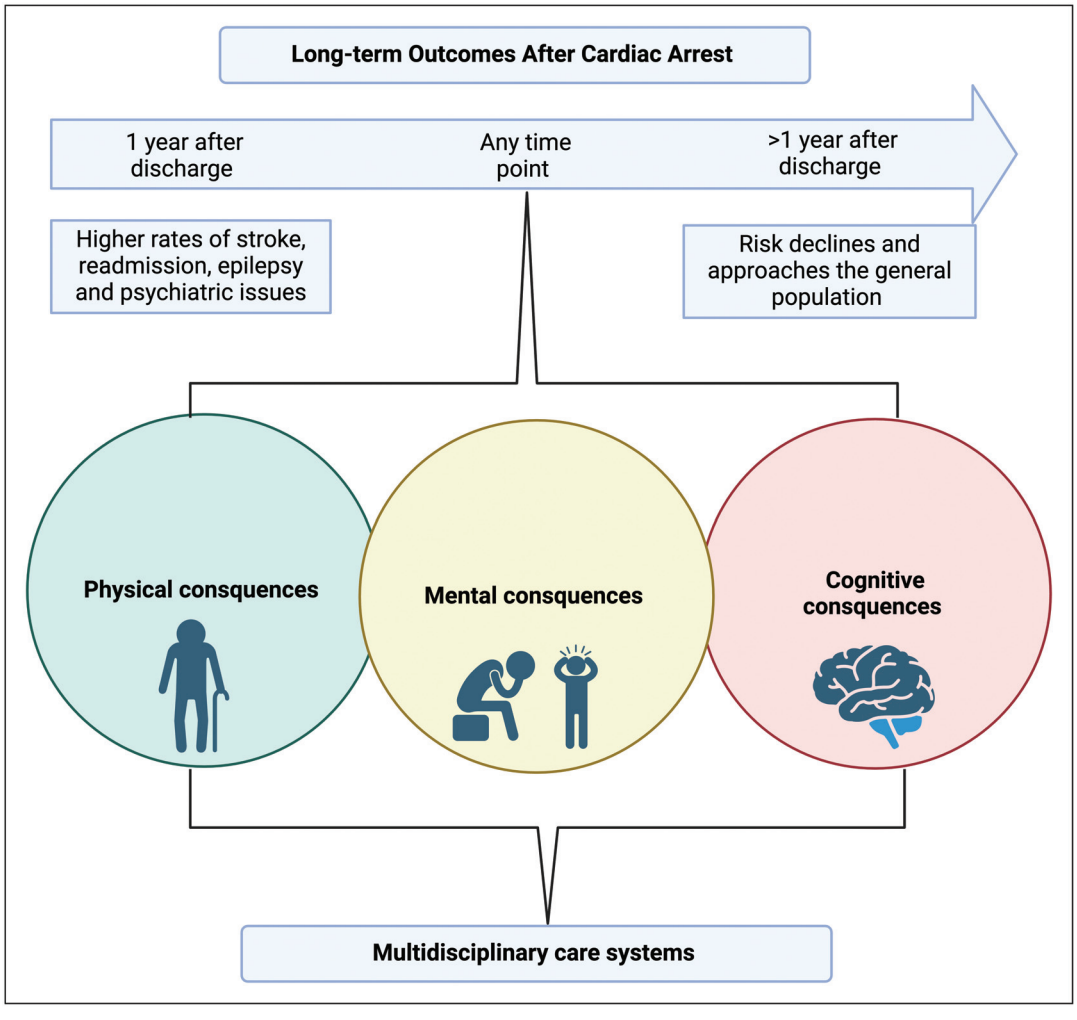
Long-term Outcomes After Cardiac Arrest
1 year after discharge
Any time point
>1 year after discharge
Higher rates of stroke, readmission, epilepsy and psychiatric issues
Risk declines and approaches the general population
Physical consquences
Mental consquences
Cognitive consquences
Multidisciplinary care systems

FIGURE 1. Long-term consequences of cardiac arrest. Cardiac arrest survivors may experience long-term consequences that affect their physical, cognitive, and mental domains. In addition, they exhibit higher rates of stroke, readmission, epilepsy, and psychiatric issues than the general population during the first year after discharge, as noted by Secher *et al.* (2022). Notably, this risk declines after the one-year mark.

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Two recent systematic reviews and meta-analyses evaluated long-term survival outcomes in OOHCA until 15 years after hospital discharge [34▪,35]. Chin and coworkers showed a 77.3% survival at 1 year and 20.8% at 15 years ($n = 155\ 909$) [34▪] Amecher *et al.* revealed a 57.5% survival rate at 15 years (n = 11 800) [35]. These studies are essential as they revealed a variety of interesting facts. In the first study, the survival rate at 1 year was more significant in Europe and North America. [34▪] Furthermore, noncardiac causes of cardiac arrest had higher survival rates at all time points, and survival with good neurological outcome at 1 year ($n = 6534$) occurred in 83.3% of patients [34▪]. In this same study, men were 1.4 times more likely than women to survive to the 1-year mark [34▪].

Poor neurological outcome at discharge

Determining long-term outcomes for patients with poor neurological status (CPC 3 and 4) at discharge following cardiac arrest poses a challenge, primarily due to the potential for these patients to undergo withdrawal of life-sustaining treatment (WLST). Information concerning outcomes unaffected by WLST largely stems from countries where this practice is either restricted or infrequent. A recent study conducted in Japan, where the impact of WLST is minimal, showed that out of 1012 patients admitted after OOHCA, 239 had poor neurological outcomes at discharge (CPC 3 or 4); of these, 3.6% improved to CPC 1 or 2 at 6 months and 28.4% died in the first 6 months. In addition, no improvement was seen after 6 months. Of the patients with CPC 3, 31% fully recovered, while only 1.3% of the patients with CPC 4 at hospital discharge improved to CPC 2; in total, only a total of nine patients with poor neurological outcome at discharge achieved improvement at 6 months. The rate of survival in patients with poor neurological outcomes was approximately 1 year [36▪]. In a retrospective observational study in Korea that included 279 OOHCA survivors, 33.3% survived until 1-month follow-up, and 22.6% died before 6 months; these were the patients that had a CPC of 3 or 4 at 1-month follow-up. Of the patients who survived in the CPC 3 category, 16.2% showed improvement. However, no improvement was seen for those with a CPC score of 4 [37]. A German study involving 89 survivors with a CPC score of 4 found no neurological improvement at a median of 81 months in 97% of individuals of the 61 that completed follow up [38]. In the United States, a study conducted among patients with severe disability at hospital discharge revealed a 1-year mortality rate of 89% in patients who were discharged into hospice facilities and 38% among individuals who were discharged into rehabilitation and acute care facilities, in addition, this group also presented frequent hospital readmissions within 1 year [39].

Outcomes in older adults

Advanced age often correlates with poorer functional status preceding cardiac arrest, which can exacerbate the challenges of CPR. Consequently, older adults facing cardiac events may experience diminished survival rates and an increased risk of adverse neurological outcomes [40]. Marcus *et al.* showed worse survival rates at hospital discharge and long-term follow-up (average follow-up was 5 years) for adults aged over 80. Additionally, achieving a favorable functional status upon hospital discharge (CPC 1 or 2) was notably lower in older patients (32.2%) compared to their younger counterparts (60.7%) [40]. Moreover, prearrest conditions significantly influence mortality rates, as demonstrated in a study linking frailty to increased mortality, in which 30-day survival rate was 5.6% and only 1.1% of elderly patients achieved a good neurological outcome [41]. While age is undoubtedly a factor in survival rates among the elderly, preexisting conditions wield considerable influence over neurological outcomes postcardiac arrest. Consequently, there remains a substantial challenge in determining which elderly patients stand to benefit from full resuscitation efforts, as opposed to potentially prolonging their suffering.

COMPREHENSIVE SYSTEMS OF CARE AFTER HOSPITAL DISCHARGE

In 2020, the American Heart Association (AHA) issued a statement regarding sudden cardiac arrest survivorship, highlighting the necessity for comprehensive systems of care posthospital discharge [42]. These systems encompass patients, caregivers, and rehabilitation services, with a focus on identifying and addressing gaps in medical care for cardiac arrest survivors. It provides roadmap approach for the care of patients, including ultra-short-term, short-term, medium-term, and long-term interventions, as well as a discharge checklist aimed at promoting multidisciplinary care for patients that involves rehabilitation therapies, psychological support, medication management, and ongoing medical monitoring [42].

One study identified several barriers that limit the implementation of cognitive impairment screening strategies and rehabilitation programs in cardiac arrest survivors, including the lack of clear instructions in guidelines, decreased knowledge of the consequences of cardiac arrest by specialties, lack of awareness by patients burden to patients

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of early screening, financial insecurities and insurance procedures and lack of collaborations between specialists [43]. These limitations prove the need for establishing multidisciplinary and comprehensive care systems, along with rehabilitation programs, to increase HRQoL in survivors of cardiac arrest. A study conducted in Norway revealed an increase in the usage of healthcare systems after cardiac arrest; specifically, the use of rehabilitation systems increased from 2% (2 years before the event) to 38% one year after the event. Notably, at 1 year, 4% of patients who were referred for rehabilitation services were still waiting to start [44▪].

CONCLUSION

In conclusion, while interventions targeting HIBI show promise, none have consistently improved outcomes beyond early assessment periods. Targeted temperature management has yielded mixed results, as it may improve short-term outcomes, but there is limited information on its efficacy regarding long-term outcomes. Furthermore, prognostication guidelines primarily rely on short-term studies, indicating a gap in understanding long-term outcomes.

Long-term recovery after cardiac arrest presents several challenges; survivors often experience physical, cognitive, and mental health issues. Comprehensive and multidisciplinary care systems are essential to address these challenges and enhance HRQoL. Despite some improvements in outcomes, cardiac arrest survivors still experience higher mortality and readmission risks than the general population, highlighting the need for further research to understand and address cardiac arrest, focusing on the prediction of long-term rather than short-term outcomes.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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In this cohort study, cardiac arrest survivors were compared to a myocardial infarction cohort and to the general population. The total sample size of the study was 250 838 patients, which were divided in to three different groups. The study showed that cardiac arrest survivors had an increased rate of stroke, epilepsy, and psychiatric conditions during the first year after hospital discharge. In addition, it showed an increased risk for developing dementia than the comparison cohorts.

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This retrospective study evaluated recovery in patients who survived cardiac arrest with a poor neurological outcome at hospital discharge, defined by a CPC score of 3 or 4. Findings revealed that only 3.6% had neurological improvement during the first 6 months, and was more significant in those with a CPC score of 3 at hospital discharge.

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This retrospective study identified an increase in health-care utilization after cardiac arrest, specifically in the areas of primary care, specialists and mental healthcare services.

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